REMARKS

Claims 17-18, 21-38 and 41 are currently pending in the application. Claims 1-16, 19, 20, 39 and 40 are canceled. Claims 18, 21 and 24 are amended. New claims 42-45 are added. The amendments find support in the specification and are discussed in the relevant sections below. No new matter is added.

The Examiner states at page 6 of the Office Action that claims 32 and 33 would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Applicants have added new claims 42 through 45 accordingly.

Claim Objections

The Examiner has objected to claim 24 for the recitation of "labeled". Claim 24 has been amended to remove the term "labeled."

Rejection of Claim 17 Under 35 U.S.C. §102(b)

The Examiner has maintained the rejection of claim 17 under 35 U.S.C. §102(b) as being allegedly anticipated by Fitzpatrick et. al. (US Pat. 5,710,009).

Applicants respectfully traverse the rejection.

Applicants submit that for a determination of anticipation to be proper, the prior art reference must disclose each and every limitation of the claim. *Atlas Powder Company et al. v. IRECO, Incorporated et al.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999).

Claim 17 of the instant application claims "**a polypeptide pair comprising a first polypeptide immobilized to a support, and a second binding partner polypeptide bound to the first polypeptide**, wherein the binding of the polypeptides to each other is detectable, and **covalent modification of at least one of the polypeptides results in modulation of the binding, and is required for said binding of said first polypeptide and said second binding partner polypeptide**, and wherein said covalent modification comprises one of the group consisting of phosphorylation, dephosphorylation, acylation, deacylation, glycosylation,

deglycosylation, ubiquitination, deubiquitination, prenylation, deprenylation, sentrinization, desentrinization, ADP-ribosylation and ADP-deribosylation." (Emphasis added)

The Fitzpatrick et al. reference teaches a reland-biotin complex. Example 3 (column 28) of the Fitzpatrick et al. reference describes "the ability of the reland biotin complex to be released by Hb [hemoglobin] and Hb Glc [glycated hemoglobin]". In particular, example 3 of the Fitzpatrick reference teaches that **non-glycated** reland biotin can form an antibody:reland complex with a monoclonal antibody specific for human **glyco**hemoglobin (Clone B, described at column 27, lines 32 through 36). The Fitzpatrick et al. reference teaches a competition assay wherein the association of **non-glycated** reland biotin with an antibody specific for human **glyco**hemoglobin is modulated by the presence of a competitor molecule, in this case glycated hemoglobin. In particular, example 3 of the Fitzpatrick et al. reference discloses that "[g]lycated hemoglobin was able to release significant amount of the antibody bound to reland." (Column 28, lines 57 through 58).

The Examiner states at page 3 of the Office Action that "Fitzpatrick et al disclose and claim a composition that comprises an immobilized complex (see claim 19) that comprises the combination of first and second polypeptides, specifically a peptide 'reland' (col. 5, lines 4-6, line 22) together with its receptor (see col. 5, lines 54-60), wherein the two polypeptides of Fitzpatrick et al of (Example 3, col. 27) are the combination of a deglycoslyated hemoglobin and an antibody that binds to covalently modified/glycosylated hemoglobin."

Applicants submit that neither of the non-glycalated reland-biotin conjugate or the monoclonal antibody specific for human glycohemoglobin taught in the Fitzpatrick reference is covalently modified as required by instant claim 17. Binding of the non-glycalated reland-biotin conjugate to an antibody specific for human glycohemolobin is therefore not modulated by covalent modification of at least one of the polypeptides and does not require covalent modification of at least one of the polypeptides, also as required by instant claim 17.

The Fitzpatrick et al. reference therefore does not teach "**a polypeptide pair comprising a first polypeptide immobilized to a support, and a second binding partner polypeptide bound to the first polypeptide**, wherein the binding of the polypeptides to each other is

detectable, and **covalent modification of at least one of the polypeptides results in modulation of the binding, and is required for said binding of said first polypeptide and said second binding partner polypeptide**, and wherein said covalent modification comprises one of the group consisting of phosphorylation, dephosphorylation, acylation, deacylation, glycosylation, deglycosylation, ubiquitination, deubiquitination, prenylation, deprenylation, sentrinization, desentrinization, ADP-ribosylation and ADP-deribosylation, as required by instant claim 17. (Emphasis added)

In view of the above, Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection of Claims 17, 18, 21-26, 31 and 34-38 Under 35 U.S.C. §102(b)

Claim 17

The Examiner has maintained the rejection of claim 17 under 35 U.S.C. 102(b) for allegedly being anticipated by Hochstrasser et al (US Pat. 5,565,352).

Applicants respectfully traverse the rejection.

Applicants submit that for a determination of anticipation to be proper, the prior art reference must disclose each and every limitation of the claim. *Atlas Powder Company et al. v. IRECO, Incorporated et al.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999).

Claim 17 recites, "a polypeptide pair comprising a first polypeptide immobilized to a support, and a second binding partner polypeptide bound to the first polypeptide, wherein the binding of the polypeptides to each other is detectable, and **covalent modification of at least one of the polypeptides results in modulation of the binding, and is required for said binding of said first polypeptide and said second binding partner polypeptide**, and wherein said covalent modification comprises one of the group consisting of phosphorylation, dephosphorylation, acylation, deacylation, glycosylation, deglycosylation, ubiquitination, deubiquitination, prenylation, deprenylation, sentrinization, desentrinization, ADP-ribosylation and ADP-deribosylation."

The Examiner states at page 4 of the Office Action that "[i]t is the position of the example that the immobilized complex (see Figure 6a) was the combination of first and second polypeptides. The first polypeptide being an ubiquitin-oligopeptide covalent conjugate and the second polypeptide being an antiubiquitin antibody polypeptide. (see col. 1, lines 23-25, and lines 26-45)...(see Figures 6a and 6b) [t]he immobilized ubiquitin-oligopeptide covalent conjugate formed a complex on a solid immunoblot surface when immunoreacted with an anti-ubiquitin antibody polypeptide; also see col. 6, lines 63-67 and col. 7, lines 1-16; Example 4, col. 40, lines 14-56)...[t]he reference still anticipates the instantly claimed complex that comprises first and second polypeptides to comprise a covalent modification, specifically ubiquitination, in order to form a complex."

The Hochstrassser et al. reference teaches an-anti ubiquitin antibody bound to an immobilized ubiquitin-oligopeptide. Neither of the anti-ubiquitin antibody or the immobilized ubiquitin-oligopeptide are "covalently modified" as required by instant claim 17. The Hochstrasser et al. reference therefore does not teach "**a polypeptide pair comprising a first polypeptide immobilized to a support, and a second binding partner polypeptide bound to the first polypeptide**, wherein the binding of the polypeptides to each other is detectable, and **covalent modification of at least one of the polypeptides results in modulation of the binding, and is required for said binding of said first polypeptide and said second binding partner polypeptide**, and wherein said covalent modification comprises one of the group consisting of phosphorylation, dephosphorylation, acylation, deacylation, glycosylation, deglycosylation, ubiquitination, deubiquitination, prenylation, deprenylation, sentrinization, desentrinization, ADP-ribosylation and ADP-deribosylation" as required by instant claim 17. (Emphasis added)

In view of the above, Applicants respectfully request reconsideration and withdrawal of the rejection.

Claims 18, 21-26, 31 and 34-38

The rejection of claims 18, 21-26, 31, and 34-38 under 35 U.S.C. 102(b) as being allegedly anticipated by Hochstrasser et al (US Pat. 5,565,352) is maintained.

Applicants respectfully traverse the rejection.

The Examiner asserts at pages 4 through 10 of the office action that "Hoshstrasser et al disclose an assay of a polypeptide substrate modified by polyubiquitin, which is proteolytically digested and further modified by the disclosed deubiquitination enzyme (see Figure 6b)...The assay for agonists/antagonists/modulators (see col. 25, lines 30-51) of activity are disclosed to include a candidate substance (see col. 26, lines 13-15) which are combined with the first polypeptide, a substrate second polypeptide/protein, co-factors, relevant modifications such as glycosylation or prenylation...The first polypeptide, deubiquitin is disclosed for immobilization on a solid support (see col. 26, lines 66-67 bridging to col. 27, lines 1-5)...[a]mong the disclosed second polypeptide are "short-lived eukaryotic proteins...[t]he modifying enzyme which attaches ubiquitin to the substrate protein/polypeptide is E2 enzymes (see col. 33, lines 53-59)...E2 enzymes (see col. 33, lines 55-59) are modifying enzymes that covalently attach and modify the second short lived polypeptide with ubiquitin (see col. 33, lines 29-31). The combination of polypeptide-ubiquitin conjugate defines a species of second polypeptide disclosed in '352; the conjugate being made through the action of a modification enzyme E2 (adds ubiquitin to a polypeptide) and the modifying substrate."

Applicants submit that for a determination of anticipation to be proper, the prior art reference must disclose each and every limitation of the claim. *Atlas Powder Company et al. v. IRECO, Incorporated et al.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999).

Claim 18 recites "a method for detecting or monitoring the activity of a modulator of a polypeptide modification enzyme, comprising the steps of: providing a **first polypeptide**, and a **second polypeptide**, wherein at least one of the polypeptides is susceptible to covalent modification, and the first and second polypeptides are capable of binding to each other, and said covalent modification of one or both of the polypeptides by the **modification enzyme** in the presence of a **modifying group substrate** results in modulation of the binding of the polypeptides to each other; allowing the polypeptides to bind to each other; contacting the polypeptides with a modification enzyme in the presence of said modifying group substrate; detecting modulation of the binding of the polypeptides to determine a reference signal modulation, contacting the polypeptides with a modification enzyme and a candidate modulator of the modification enzyme, and detecting modulation of binding of the polypeptides in the

presence of said candidate modulator, and comparing the modulation detected in the presence of said candidate modulator with the reference signal modulation."

That is, claim 18 requires 1) a polypeptide modification enzyme, 2) a first polypeptide, 3) a second polypeptide and 4) a modifying group substrate.

The Hochstrasser et al. reference teaches "[t]he attachment of ubiquitin to proteins is catalyzed by ubiquitin-conjugating enzymes." (see column 33, lines 55 through 57). The Hochstrasser et al. reference also teaches that "the enzyme of the present invention can be coupled to a solid support." The Hochstrasser et al. reference also teaches that "many short-lived eukaryotic proteins, covalent attachment to the polypeptide ubiquitin is a prerequisite for their degradation." (see column 34, lines 30 through 32). That is, the Hochstrasser et al. reference teaches a ubiquitin conjugating enzyme (which can be coupled to a solid support), a short lived protein which can be ubiquitinated and ubiquitin. The Hochstrasser et al. reference does not teach "a method for detecting or monitoring the activity of a modulator of a polypeptide modification enzyme" that requires the combination of 1) a polypeptide modification enzyme, 2) a first polypeptide, 3) a second polypeptide and 4) a modifying group substrate as required by instant claim 18.

The Hochstrasser et al. reference therefore does not teach "a method for detecting or monitoring the activity of a modulator of a **polypeptide modification enzyme**, comprising the steps of: providing a **first polypeptide**, and a **second polypeptide**, wherein at least one of the polypeptides is susceptible to covalent modification, and the first and second polypeptides are capable of binding to each other, and said covalent modification of one or both of the polypeptides by the modification enzyme in the presence of a **modifying group substrate** results in modulation of the binding of the polypeptides to each other; allowing the polypeptides to bind to each other; contacting the **polypeptides** with a **modification enzyme** in the presence of said **modifying group substrate**; detecting modulation of the binding of the polypeptides to determine a reference signal modulation, contacting the **polypeptides** with a **modification enzyme** and a candidate modulator of the modification enzyme, and detecting modulation of binding of the polypeptides in the presence of said candidate modulator, and comparing the

modulation detected in the presence of said candidate modulator with the reference signal modulation" as required by claim 18. (Emphasis added)

Amended claim 21 claims "a method for detecting, in a sample, the presence of a modifying enzyme which covalently modifies a first polypeptide, the method comprising the steps of: a) providing **a first polypeptide immobilized on a support, wherein said first polypeptide comprises a binding site to which a second polypeptide specifically binds**, wherein said second polypeptide is not a phospho-specific antibody, and **wherein covalent modification of said first polypeptide detectably changes the association of said first and second polypeptide**; b) providing said second polypeptide and said test sample in the presence of a modifying group substrate, and contacting said second polypeptide and said test sample with said first polypeptide immobilized on a support; c) measuring association of said first polypeptide with said second polypeptide; and d) comparing said association with the association of a first and second polypeptide contacted with a control sample known to contain said modifying enzyme and said modifying group substrate wherein a change in the association of said first and second polypeptide determined in step (c) relative to said association determined in step (d) provides an indicator of the presence of the enzyme in said test sample.

As discussed above, the Hochstrasser et al. reference teaches immobilized ubiquitin-oligopeptide or "the [ubiquitin conjugating] enzyme of the present invention can be coupled to a solid support."

The Hochstrasser et al. reference does not teach "a method for detecting, in a sample, the presence of a modifying enzyme which covalently modifies a first polypeptide" that requires "**a first polypeptide immobilized on a support, wherein said first polypeptide comprises a binding site to which a second polypeptide specifically binds**, wherein said second polypeptide is not a phospho-specific antibody, and **wherein covalent modification of said first polypeptide detectably changes the association of said first and second polypeptide**" as required by instant claim 21.

Claim 22 claims "a method for detecting, in a sample, the presence of a modifying enzyme which covalently modifies a polypeptide, the method comprising the steps of: a) providing a polypeptide pair comprising a **first polypeptide** and a **second, binding partner**

polypeptide, capable of associating with said first polypeptide, wherein said second, binding partner polypeptide is not a phospho-specific antibody, and wherein the association of the polypeptides is detectable, and covalent modification of at least one of the polypeptides results in modulation of the association and wherein said covalent modification comprises one of the group consisting of phosphorylation, acylation, glycosylation, ubiquitination, prenylation, sentrinization, and ADP-ribosylation; b) providing a **modifying group substrate**, wherein said substrate, in the presence of a **modifying enzyme**, results in the covalent modification of said first polypeptide or said second binding partner polypeptide; c) **immobilizing the first polypeptide to a physical support**; d) contacting said immobilized polypeptide and said second binding partner polypeptide in the presence of said sample and said modifying group substrate; and; e) measuring the association of the second, binding partner polypeptide to the first polypeptide, thereby determining the covalent modification of at least one of said polypeptides, whereby the presence of said modifying enzyme is detected.

Claim 22 requires 1) a modifying enzyme, 2) a first polypeptide, 3) a second polypeptide and 4) a modifying group substrate.

The Hochstrasser et al. reference does not teach "a method for detecting, in a sample, the presence of a modifying enzyme which covalently modifies a polypeptide" that requires the combination of 1) a first polypeptide; 2) a second polypeptide; 3) a modifying group substrate; and 4) a modifying enzyme. Further, although the Hochstrasser et al. reference teaches immobilized ubiquitin-oligopeptide or "the [ubiquitin conjugating] enzyme of the present invention can be coupled to a solid support" the Hochstrasser et al. reference does not teach "a method for detecting, in a sample, the presence of a modifying enzyme which covalently modifies a polypeptide" that requires "**immobilizing the first polypeptide to a physical support**" as required by claim 22 and dependent claims 24, 25, 26, 31, 36, 37 and 38.

Claim 23 claims "a method for detecting, in a sample, the presence of a modifying enzyme which covalently modifies a polypeptide, the method comprising the steps of: a) providing a polypeptide pair comprising a first polypeptide and a **covalently modified second, binding partner polypeptide** capable of associating with said first polypeptide, wherein said second, binding partner polypeptide is not a phospho-specific antibody, and wherein said

association of the polypeptides is detectable, and wherein removal of the covalent modification from said second, binding partner polypeptide by a modifying enzyme results in modulation of the association and wherein said covalent modification comprises one of the group consisting of phosphorylation, acylation, glycosylation, ubiquitination, prenylation, sentrinization, and ADP-ribosylation; b) immobilizing the first polypeptide to a physical support; c)contacting said immobilized polypeptide and said second binding partner polypeptide in the presence of said sample; and d) measuring the association of the second, binding partner polypeptide to the first polypeptide, thereby determining the removal of said covalent modification from said second binding partner polypeptide, whereby the presence of said modifying enzyme is detected."

The Hochstrasser et al. reference does not teach a "a method for detecting, in a sample, the presence of a modifying enzyme which covalently modifies a polypeptide" that requires "**a covalently modified second, binding partner polypeptide**," as required by claim 23. Although the Hochstrasser et al. reference teaches immobilized ubiquitin-oligopeptide or "the [ubiquitin conjugating] enzyme of the present invention can be coupled to a solid support" the Hochstrasser et al. reference also does not teach "a method for detecting, in a sample, the presence of a modifying enzyme which covalently modifies a polypeptide" that requires "**immobilizing the first polypeptide to a physical support**" as required by claim 23 and dependent claims 24, 25, 26, 31, 36, 37 and 38.

Claim 34 claims "a method for detecting, in a sample, the presence of a **modifying enzyme** which covalently modifies a polypeptide, the method consisting of the steps, in the sequence set forth of: a) providing a polypeptide pair comprising a **first polypeptide** and a **second, binding partner polypeptide** capable of associating, wherein said second, binding partner polypeptide is not a phospho-specific antibody, and wherein the association of the polypeptides is detectable, and covalent modification of at least one of the polypeptides results in modulation of the association and wherein said covalent modification comprises one of the group consisting of phosphorylation, acylation, glycosylation, ubiquitination, prenylation, sentrinization, and ADP-ribosylation; b) providing **a modifying group substrate**, wherein said substrate, in the presence of a modifying enzyme, results in the covalent modification of said first polypeptide or said second binding partner polypeptide; c) **immobilizing the first polypeptide to a physical support**; d) contacting said immobilized polypeptide and said second

binding partner polypeptide in the presence of said sample and said modifying group substrate; and e) measuring the association of the second, binding partner polypeptide to the first polypeptide, by contacting said binding partner polypeptide with an antibody that binds to said binding partner polypeptide, thereby determining the covalent modification of at least one of said polypeptides, whereby the presence of said modifying enzyme is detected.

In particular, claim 34 requires the combination of 1) a sample comprising a modifying enzyme; 2) a first polypeptide; 3) a second, binding partner polypeptide; and 4) a modifying group substrate.

The Hochstrasser et al. reference does not teach "a method for detecting, in a sample, the presence of a modifying enzyme which covalently modifies a polypeptide" that requires the combination of 1) a sample comprising a modifying enzyme; 2) a first polypeptide; 3) a second, binding partner polypeptide; and 4) a modifying group substrate. Further, although the Hochstrasser et al. reference teaches immobilized ubiquitin-oligopeptide or "the [ubiquitin conjugating] enzyme of the present invention can be coupled to a solid support" the Hochstrasser et al. reference does not teach "**immobilizing the first polypeptide to a physical support**" as required by claim 34.

Claim 35 claims "a method for detecting, in a sample, the presence of a modifying enzyme which covalently modifies a polypeptide, the method comprising the steps of, in the sequence set forth: a) providing a polypeptide pair comprising a first polypeptide and a **covalently modified second, binding partner polypeptide** capable of associating, wherein said second, binding partner polypeptide is not a phospho-specific antibody, and wherein said association of the polypeptides is detectable, and wherein removal of the covalent modification from said second, binding partner polypeptide by a modifying enzyme results in modulation of the association and wherein said covalent modification comprises one of the group consisting of phosphorylation, acylation, glycosylation, ubiquitination, prenylation, sentrinization, and ADP-ribosylation; b) **immobilizing the first polypeptide to a physical support**; c) contacting said immobilized polypeptide and said second binding partner polypeptide in the presence of said sample; and d) measuring the association of the second, binding partner polypeptide to the first polypeptide, using an antibody that binds to said binding partner polypeptide, thereby

determining the removal of said covalent modification from said second binding partner polypeptide, whereby the presence of said modifying enzyme is detected."

The Hochstrasser et al. reference does not teach "a method for detecting, in a sample, the presence of a modifying enzyme which covalently modifies a polypeptide" that requires a **covalently modified second, binding partner polypeptide**, as required by claim 35. Although the Hochstrasser et al. reference teaches immobilized ubiquitin-oligopeptide or "the [ubiquitin conjugating] enzyme of the present invention can be coupled to a solid support" the Hochstrasser et al. reference does not teach "**immobilizing the first polypeptide to a physical support**" as required by claim 35.

In view of all of the above, Applicants submit that claims 17, 18, 21-26, 31 and 34-38 are novel in view of the Hochstrasser et al. reference. Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection of Claims 17 and 41 Under 35 U.S.C. §112

The Examiner has rejected claim 21 for insufficient antecedent basis for the limitation "test".

Applicants have amended claim 21 to delete the term test thereby rendering the rejection moot.

In view of the above, Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection of Claims 17 and 41 Under 35 U.S.C. §102(b)

Claims 17 and 41 are rejected under 35 U.S.C. 102(b) as being alleged anticipated by Avruch et al (US Pat. 5,582,995) in light of Avruch et al (US Pat. 5,736,337).

Applicants respectfully traverse the rejection.

Applicants submit that for a determination of anticipation to be proper, the prior art reference must disclose each and every limitation of the claim. *Atlas Powder Company et al. v. IRECO, Incorporated et al.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999).

Claims 17 and 41 claim "a polypeptide pair comprising a first polypeptide immobilized to a support, and a second binding partner polypeptide bound to the first polypeptide, wherein the binding of the polypeptides to each other is detectable, and **covalent modification of at least one of the polypeptides results in modulation of the binding, and is required for said binding of said first polypeptide and said second binding partner polypeptide**." (Emphasis added)

The Examiner states at pages 7 through 8 of the Office Action that "Avruch et al disclose the instantly claimed invention directed to a polypeptide pair comprising a first polypeptide immobilized to a support and a second polypeptide bound to the first polypeptide, wherein binding of the two polypeptide is detectable...Avruch et al disclose an immobilized polypeptide pair complex, the first polypeptide being Ras or a Raf-binding fragment thereof bound to Raf or a Ras-binding fragment thereof (see col. 14, lines 13-21)...Avruch et al disclose a polypeptide pair comprising: A **first polypeptide** immobilized to the support (either Raf (a kinase, see col. 13, line 20)) or Ras (see col. 13, lines 40-60); and A **second binding partner polypeptide** bound to the first polypeptide (if Raf is immobilized then Ras is the second binding partner polypeptide or if Ras is immobilized then Raf is the second binding partner polypeptide (see col. 6, lines 1-65)) , wherein modulation of binding is effected by a covalent modification, the covalent modification (see col. 16, lines 25-35 "acetylation or carboxylation", "glycosylation", "deglycoylationg", "phosphorylated") being a phosphate group results in phosphorylation, the complex being immobilized through binding the first and second polypeptide to each other (see col. 16, lines 64-67 and col. 17, lines 1-3) and to a solid phase by the first polypeptide, wherein the binding of the first and second polypeptides is detectable with a monoclonal antibody (see col. 4, lines 58-59), or the second polypeptide is labeled (see col. 13, lines 64-65)..

The Examiner concludes that " the immobilized complex [that] comprises first and second polypeptides of a polypeptide pair of Avruch et al **inherently** anticipates the instantly claimed invention in light of the evidence provided by Avruch et al '337 that shows modulation of binding between the two polypeptides based upon phosphorylation (see '337, col. 20, lines 1-15), and dephosphorylation would modulate binding."

Applicants submit that the '995 patent teaches a method of screening for compounds which inhibit the direct binding of Ras or Raf-binding fragments to Raf or Ras binding fragments (see abstract).

Neither of the Avruch et al. references teach that covalent modification of at least one of Ras or Raf binding fragments results in modulation of the binding **and** is required for the binding of Ras and Raf binding fragments.

Neither of the Avruch et al. references teach "a polypeptide pair comprising a first polypeptide immobilized to a support, and a second binding partner polypeptide bound to the first polypeptide, wherein the binding of the polypeptides to each other is detectable, and **covalent modification of at least one of the polypeptides results in modulation of the binding, and is required for said binding of said first polypeptide and said second binding partner polypeptide" as required by instant claims 17 and 41.**

Inherency

The Examiner states at page 8 of the Office Action that "the immobilized complex [that] comprises first and second polypeptides of a polypeptide pair of Avruch et al **inherently** anticipates the instantly claimed invention in light of the evidence provided by Avruch et al '337 that shows modulation of binding between the two polypeptides based upon phosphorylation (see '337, col. 20, lines 1-15), and dephosphorylation would modulate binding."

Applicants submit that the Examiner must provide rationale or evidence tending to show inherency to properly make a rejection under 35 U.S.C. 102 when the prior art is silent as to an inherent characteristic (MPEP §2112).

The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) ...; *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. **Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result**

from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (Emphasis) (MPEP §2112, citations omitted).

The '337 patent states that "[p]hosphorylation of the Raf[1-149] fragment on serine 43 by cAMP-dependent protein kinase substantially reduced Ras binding, demonstrating that downregulation of the Ras-Raf pathway by cAMP occurs exclusively through the first 149 amino acids of the c-Raf-1 regulatory domain and does not require full length Raf protein. These data suggest a model of PKA-dependent regulation in which phosphorylation of c-Raf-1 serine 43 induces a protein flap containing residues 1-50 to block the Ras docking site on c-Raf-1."

Applicants submit that neither of the '995 or '337 references teach a polypeptide pair that is inherently "a polypeptide pair comprising a first polypeptide immobilized to a support, and a second binding partner polypeptide bound to the first polypeptide, wherein the binding of the polypeptides to each other is detectable, and **covalent modification of at least one of the polypeptides results in modulation of the binding, and is required for said binding of said first polypeptide and said second binding partner polypeptide**" as required by instant claims 17 and 41.

Applicants submit that one of skill in the art would not accept that the ras and raf binding fragments disclosed in the '995 patent are inherently "a polypeptide pair comprising a first polypeptide immobilized to a support, and a second binding partner polypeptide bound to the first polypeptide, wherein the binding of the polypeptides to each other is detectable, and **covalent modification of at least one of the polypeptides results in modulation of the binding, and is required for said binding of said first polypeptide and said second binding partner polypeptide**" as required by instant claims 17 and 41.

In view of all of the above, one of skill in the art would not accept that it is necessarily probable or possible that the ras and raf binding fragments of the WO '995 patent are inherently "a polypeptide pair comprising a first polypeptide immobilized to a support, and a second binding partner polypeptide bound to the first polypeptide, wherein the binding of the polypeptides to each other is detectable, and **covalent modification of at least one of the polypeptides results in modulation of the binding, and is required for said binding of said**

first polypeptide and said second binding partner polypeptide" as required by instant claims 17 and 41.

One of skill in the art would also not accept that it is necessarily probable or possible that the ras and raf binding fragments of the WO '995 patent are inherently "a polypeptide pair comprising a first polypeptide immobilized to a support, and a second binding partner polypeptide bound to the first polypeptide, wherein the binding of the polypeptides to each other is detectable, and **covalent modification of at least one of the polypeptides results in modulation of the binding, and is required for said binding of said first polypeptide and said second binding partner polypeptide**" as required by instant claims 17 and 41.

Applicants respectfully submit that the Examiner has not provided extrinsic evidence that makes clear that "the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill".

In view of the above, Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection of Claims 17, 18, 21-27, 31 and 41, Under 35 U.S.C. §102(e)

Claims 17 and 41 are rejected under 35 U.S.C. 102(e) as being allegedly anticipated by Beach et al (U.S. 6,037,136).

Applicants respectfully traverse the rejection.

Applicants submit that for a determination of anticipation to be proper, the prior art reference must disclose each and every limitation of the claim. *Atlas Powder Company et al. v. IRECO, Incorporated et al.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999).

Claims 17 and 41

Claims 17 and 41 claim "a polypeptide pair comprising a first polypeptide immobilized to a support, and a second binding partner polypeptide bound to the first polypeptide, wherein the binding of the polypeptides to each other is detectable, and **covalent modification of at least one of the polypeptides results in modulation of the binding, and is required for said binding of said first polypeptide and said second binding partner polypeptide.**" (Emphasis added).

The Examiner states at page 9 of the Office Action that "Beach et al disclose a polypeptide pair comprising: A first polypeptide immobilized to the support (either Raf (a kinase)) or CDC25 (a phosphatase, see col. 9, line 44) , see col. 10, lines 35-57 and col. 11, lines 1-50); and A second binding partner polypeptide bound to the first polypeptide (if Raf is immobilized then CDC25 is the second binding partner polypeptide or if CDC25 is immobilized then Raf is the second binding partner polypeptide), wherein modulation of binding is effected by a covalent modification, the covalent modification being the transfer of a phosphate group (ATP) which results in phosphorylation (see col. 6, lines 15-29, col. 6, lines 56-61; col. 12, lines 55-60 (reaction mixture includes ATP); Wherein Raf kinase binds to CDC25 phosphatase through the addition of a phosphate group, a covalent modification, resulting in phosphorylation of CDC25 (see col. 9, lines 40-45). Beach et al disclose the instantly claimed invention directed to an immobilized polypeptide pair, the pair including the complex of Raf/CDC25. The polypeptide pair of Beach et al anticipates the instantly claimed invention as now claimed.

The Beach et al. reference teaches assays for detecting agents which modulate the ras-dependent activation of CDC25, by affecting the binding of a CDC25 protein with Raf or Raf-associated complexes (see abstract). Applicants respectfully submit that the Examiner has mischaracterized the Beach et al. reference. The Beach et al. reference does not teach that covalent modification (in particular the Examiner suggests phosphorylation) of either of CDC25 or Raf results in modulation of the binding of CDC25 to Raf.

That is, the Beach et al. reference does not teach "a polypeptide pair comprising a first polypeptide immobilized to a support, and a second binding partner polypeptide bound to the first polypeptide, wherein the binding of the polypeptides to each other is detectable, and **covalent modification of at least one of the polypeptides results in modulation of the binding, and is required for said binding of said first polypeptide and said second binding partner polypeptide**" as required by instant claims 17 and 41.

Claims 18, 21-27 and 31

Claims 18, 21-27 and 31 are rejected under 35 U.S.C. 102(e) as being allegedly anticipated by Beach et al (US Pat. 6,037,136, effective filing date October 24, 1994).

Claim 18 of the instant application claims "a method for detecting or monitoring the activity of a modulator of a polypeptide modification enzyme" that requires "a first polypeptide, and a second polypeptide, wherein at least one of the polypeptides is susceptible to covalent modification, and the first and second polypeptides are capable of binding to each other, and **said covalent modification of one or both of the polypeptides by the modification enzyme in the presence of a modifying group substrate results in modulation of the binding of the polypeptides to each other**." (Emphasis added)

Claim 21 of the instant application claims "a method for detecting, in a sample, the presence of a modifying enzyme which covalently modifies a first polypeptide" that requires "a first polypeptide immobilized on a support, wherein said first polypeptide comprises a binding site to which a second polypeptide specifically binds, wherein said second polypeptide is not a phospho-specific antibody, and **wherein covalent modification of said first polypeptide detectably changes the association of said first and second polypeptide**." (Emphasis added)

Claim 22 and dependent claims 24-27 and 31 of the instant application claim "a method for detecting, in a sample, the presence of a modifying enzyme which covalently modifies a polypeptide" that requires "a polypeptide pair comprising a first polypeptide and a second, binding partner polypeptide, capable of associating with said first polypeptide, wherein said second, binding partner polypeptide is not a phospho-specific antibody, and **wherein the association of the polypeptides is detectable, and covalent modification of at least one of the polypeptides results in modulation of the association** and wherein said covalent modification comprises one of the group consisting of phosphorylation, acylation, glycosylation, ubiquitination, prenylation, sentrinization, and ADP-ribosylation." (Emphasis added)

Claim 23 and dependent claims 24-27 and 31 of the instant application claim "a method for detecting, in a sample, the presence of a modifying enzyme which covalently modifies a polypeptide" that requires " a polypeptide pair comprising a first polypeptide and **a covalently modified second, binding partner polypeptide capable of associating with said first polypeptide**, wherein said second, binding partner polypeptide is not a phospho-specific antibody, and wherein said association of the polypeptides is detectable, and **wherein removal of the covalent modification from said second, binding partner polypeptide by a modifying enzyme results in modulation of the association** and wherein said covalent modification

comprises one of the group consisting of phosphorylation, acylation, glycosylation, ubiquitination, prenylation, sentrinization, and ADP-ribosylation." (Emphasis added)

As discussed above, the Beach et al. reference does not teach that covalent modification of either of CDC25 or Raf (in particular the Examiner suggests phosphorylation) results in modulation of the binding of CDC25 to Raf.

The Beach et al. reference therefore does not teach any of:

"a method for detecting or monitoring the activity of a modulator of a polypeptide modification enzyme" that requires "a first polypeptide, and a second polypeptide, wherein at least one of the polypeptides is susceptible to covalent modification, and the first and second polypeptides are capable of binding to each other, and **said covalent modification of one or both of the polypeptides by the modification enzyme in the presence of a modifying group substrate results in modulation of the binding of the polypeptides to each other**" as required by instant claim 18;

"a method for detecting, in a sample, the presence of a modifying enzyme which covalently modifies a first polypeptide" that requires "a first polypeptide immobilized on a support, wherein said first polypeptide comprises a binding site to which a second polypeptide specifically binds, wherein said second polypeptide is not a phospho-specific antibody, and **wherein covalent modification of said first polypeptide detectably changes the association of said first and second polypeptide**" as required by instant claim 21; and

"a method for detecting, in a sample, the presence of a modifying enzyme which covalently modifies a polypeptide" that requires "a polypeptide pair comprising a first polypeptide and a second, binding partner polypeptide, capable of associating with said first polypeptide, wherein said second, binding partner polypeptide is not a phospho-specific antibody, and **wherein the association of the polypeptides is detectable, and covalent modification of at least one of the polypeptides results in modulation of the association** and wherein said covalent modification comprises one of the group consisting of phosphorylation, acylation, glycosylation, ubiquitination, prenylation, sentrinization, and ADP-ribosylation" as required by instant claims 22 and dependent claims 24-27 and 31.

The Beach et al. reference also does not teach "**a covalently modified second, binding partner polypeptide capable of associating with said first polypeptide**" or "a method for detecting, in a sample, the presence of a modifying enzyme which covalently modifies a polypeptide" that requires " a polypeptide pair comprising a first polypeptide and **a covalently modified second, binding partner polypeptide capable of associating with said first polypeptide**, wherein said second, binding partner polypeptide is not a phospho-specific antibody, and wherein said association of the polypeptides is detectable, and **wherein removal of the covalent modification from said second, binding partner polypeptide by a modifying enzyme results in modulation of the association** and wherein said covalent modification comprises one of the group consisting of phosphorylation, acylation, glycosylation, ubiquitination, prenylation, sentrinization, and ADP-ribosylation" as required by claim 23 and dependent claims 24-27 and 31 of the instant application.

In view of all of the above, Applicants submit that claims 1718, 21-27, 31 and 41 are novel in view of Beach et al.

Applicants respectfully request reconsideration and withdrawal of the rejection.

Claim Rejections under Obviousness-type Double Patenting

Claims 18, 21-25, 34-35 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 6,656,696. The Office Action states that although the conflicting claims are not identical, they are not patentably distinct from each other.

Claims 18 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,670,144. The Office Action states that although the conflicting claims are not identical, they are not patentably distinct from each other.

Claims 18, 21-25, and 34-35 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6,465,199. The Office Action states that although the conflicting claims are not identical, they are not patentably distinct from each other.

Claims 21-30, 34-35 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2, 4-8, 10-14 of U.S. Patent Application 09/511,776. The Office Action states that although the conflicting claims are not identical, they are not patentably distinct from each other.

Upon notification of allowance Applicants will submit terminal disclaimers to disclaim any portion of a patent issuing from the present application which would extend beyond the terms of U.S. Patent No. 6,656,696, U.S. Patent No. 6,670,144, U.S. Patent No. 6,465,199 and U.S. Patent Application 09/511,776. Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

Respectfully submitted,

Date: January 5, 2006

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